DATA EVALUATION RECORD

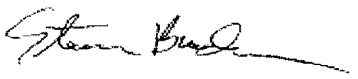
INDAZIFLAM (BCS-AA10717)

Study Type: OPPTS 870.3800 [§83-4]; Multigeneration Reproduction Study in Rats

Work Assignment No. 5-1-203 G (MRID 47443293)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Building 100, Suite B
Durham, NC 27713

Primary Reviewer: John W. Allran, M.S.	Signature:  Date: *02/20/09*
Secondary Reviewer Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *02/20/09*
Program Manager: Michael E. Viana, Ph.D., D.A.B.T.	Signature:  Date: *02/20/09*
Quality Assurance: Steven Brecher, Ph.D., D.A.B.T.	Signature:  Date: *02/20/09*

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EPA Reviewer: Alan C. Levy **Signature:** Alan C. Levy
Risk Assessment Branch 2, Health Effects Division (7509P) **Date:** 4-14-10
EPA Work Assignment Manager: Myron Ottley **Signature:** [illegible]
Risk Assessment Branch 3, Health Effects Division (7509P) **Date:** 4/16/10

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DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects Study - [rat]; OPPTS 870.3800 [§83-4]; OECD 416.

PC CODE: 080818 **DP BARCODE:** D356856
TXR#: 0054980

TEST MATERIAL (PURITY): Indaziflam (94.5% a.i.)

SYNONYMS: BCS-AA10717; AE1170437; *N*-[(1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1H-inden-1-yl]-6-[(1-fluoroethyl]-1,3,5-triazine-2,4-diamine

CITATION: Milius, A.D., Stuart, B.P. and S.G. Lake (2008) Technical Grade BCS-AA10717: a two generation reproductive toxicity study in the Wistar rat. Bayer CropScience LP, Stilwell, KS. Laboratory Study/Report Nos.: 07-R72-IH/201883, July 1, 2008. MRID 47443293. Unpublished.

Milius, A.D. and H. Hoss (2008) Technical Grade BCS-AA10717: a dose range-finding reproductive toxicity study in the Wistar rat. Bayer CropScience LP, Stilwell, KS. Laboratory Study/Report Nos.: 06-P72-GF/201879, June 25, 2008. MRID 47443315. Unpublished.

Milius, A.D. and H. Hoss (2008) BCS-AA10365: a special study to evaluate sexual maturation in female Wistar rats. Bayer CropScience LP, Stilwell, KS. Laboratory Study/Report Nos.: 07-R12-KR/201880, June 23, 2008. MRID 47443314. Unpublished.

SPONSOR: Bayer AG, Bayer CropScience, Alfred Nobel Str. 50, Monheim, Germany.

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 47443293), BCS-AA10717 (Indaziflam; 94.5% a.i.; Batch No. EFIM000511) was administered continuously in the diet to 30 Wistar rats/sex/dose group for two consecutive generations. The P generation animals were fed dietary levels of 0, 150, 1000, or 8000 ppm beginning 10 weeks prior to mating to produce the F1 litters. F1 offspring (30/sex/dose group) selected to be parents of the next generation were initially fed the same test diet concentrations as their parents. However, due to severe toxicity in the F1 offspring after weaning but before mating for the next generation (age range was 26-38 days old), the high dose of 8,000 ppm was reduced to 4,000 ppm. The average daily intake of test material during premating for P and F1 animals was 0,

10.4, 69.3 or 560.1 (P)/317.6 (F1) mg/kg/day in males and 0, 12.9, 85.2 or 656.2 (P)/355.2 (F1) mg/kg/day in females (note: at high dose, P and F1 intakes are given separately rather than averaged due to lowering of the dose to 4000 ppm). F1 parents were fed the test diets for approximately six weeks prior to mating to produce the F2 generation, and the F2 pups were maintained after weaning for evaluation of sexual maturation.

There were no mortalities and no treatment-related gross findings at necropsy at any dose in either generation. There were no adverse effects of treatment at 150 and 1000 ppm.

At 8000 ppm, coarse tremors were observed in P females at various times during premating, gestation and lactation. Body weights were decreased ($p<0.01$) in the P dams throughout **pre-mating**, resulting in a decrease of 27% (statistics not performed) in body weight gain for the pre-mating period (Weeks 0-10). Additionally in these animals, absolute food consumption was decreased ($p<0.01$) generally throughout pre-mating. In the F1 generation, body weights were decreased ($p<0.01$) throughout pre-mating in both sexes. However, these decreases were greatest at Week 0 and lessened as time progressed, and body weight gains for the pre-mating period were comparable to controls, indicating that the decreased body weights in these animals were due to their decreased weights as pups. Relative food consumption in the F1 males was decreased ($p<0.01$) for the overall (Weeks 1-10) pre-mating period. Absolute food consumption was generally decreased ($p<0.05$) throughout pre-mating in the F1 dams, with a decrease of 7% ($p<0.01$) in absolute food consumption for the overall (Weeks 1-10) pre-mating period. Body weights were decreased ($p<0.01$) throughout **gestation** in the both generations, resulting in decreases ($p<0.01$) in body weight gain for the overall gestation period of 30% and 19% compared to controls in the P and F1 generations, respectively. Body weights and absolute food consumption were decreased ($p<0.01$) throughout **lactation** in both generations.

Increased ($p<0.05$) incidences of **liver** hypertrophy and increased liver weights were observed in the 1000 ppm P males and in both sexes from both generations at 8000/4000 ppm. In the absence of other microscopic findings in the liver, the instances of hepatocellular hypertrophy and increased liver weight were considered to be an adaptive response to treatment and not adverse.

In the 8000 ppm males, absolute and relative **kidney** weights were increased ($p<0.05$) in the P generation. Hyaline degeneration in the kidneys was found in the P (15/30) and (6/30) F1 males, both compared to 0 controls. Tubular regeneration in the kidneys was observed in the P males (13 treated vs. 3 controls).

The LOAEL for parental toxicity is 8000 ppm (equivalent to 560.1/656.2 mg/kg/day in males/females, respectively) based on: coarse tremors in females, decreased body weights, body weight gains, and food consumption in both sexes and effects on the kidneys (tubular degeneration/regeneration; increased kidney weights) in the males. The NOAEL is 1000 ppm (equivalent to 69/85 mg/kg/day in males/females, respectively).

There were no treatment-related effects on pup sex ratio, organ weights, gross pathology, or histopathology, or on the birth, live birth, viability, or lactation indices at any dose in either generation. Furthermore, there were no adverse effects of treatment at 150 or 1000 ppm in any

parameter.

In the F1 pups, the following clinical signs of toxicity (# pups affected/# litters affected) were observed in the 8000/4000 ppm group: (i) pups cold to touch (1/1); (ii) perianal stain (15/9); (iii) urine stain (26/11); (iv) weak (2/1); (v) labored breathing (1/1); (vi) nasal stain (9/6); (vii) tremors (20/9); (viii) increased reactivity (2/1); (ix) distended abdomen (53/22); (x) increased activity (28/14); (xi) myoclonus (2/1); (xii) diarrhea (2/2); and (xiii) soft stool (3/3). No clinical signs of toxicity were noted in the F2 pups.

At 8000/4000 ppm, F1 pup body weights were decreased by 12-22% ($p<0.01$) compared to controls throughout the post-natal period in both sexes. Body weight gains for the overall post-natal period (PND 1-21) at this dose were decreased by 22-24% (statistics not performed).

The LOAEL for offspring toxicity is 8000/4000 ppm (reduced dosage, equivalent to average daily intakes of 317.6/355.2 mg/kg/day in males/females, respectively) based on clinical signs of toxicity, decreased body weights and body weight gains. The NOAEL is 1000 ppm (equivalent to 69/85 mg/kg/day in males/females, respectively).

The only effect on reproductive parameters was delayed sexual maturation observed in male and female F1 and F2 pups at 8000/4000 ppm compared to controls ($p<0.05$). In F1 and F2 males, preputial separation showed delays of 9.3 and 3.3 days, respectively. In F1 and F2 females, vaginal patency showed delays of 6.8 and 2.4 days, respectively. The percentage of pups reaching criterion (97-100%) was unaffected by treatment. There were no effects of treatment on estrous cycle duration or periodicity; follicle counts; the mating, fertility, and gestation indices; pre-coital interval; gestation duration; or sperm motility, counts, or morphology in either generation.

The LOAEL for reproductive toxicity is 8000/4000 ppm (reduced dosage, equivalent to average daily intakes of 317.6/355.2 mg/kg/day in males/females, respectively, based on F1 intakes), based on delayed sexual maturation in F1 and F2 pups. The NOAEL is 1000 ppm (equivalent to 69/85 mg/kg/day in males/females, respectively).

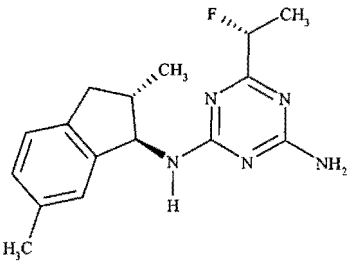
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Description:	Light beige powder
Batch #:	EFIM000511
Purity:	94.5% a.i.
Compound stability:	Stable in the diet for up to 63 days frozen or 7 days frozen followed by 7 days at room temperature.
CAS # of TGAI:	950782-86-2 (CAS # originally 730979-19-8 but renumbered effective November 2007)
Structure:	

2. Vehicle: Diet

3. Test animals

Species:	Rat	
Strain:	Wistar Hanover (Crl:WI(Glx/BRL/Han)IGS BR)	
Age at study initiation:	(P) 8 wks, (F1) 9 weeks	
Group mean body weight at study initiation:	(P) Males: 257.8 – 268.0g; Females: 167.4 – 168.8g (F1) Males: 234.7 – 302.2g; Females: 164.7 – 191.2g	
Source:	Charles River Laboratories, Raleigh, NC	
Housing:	Except during the mating phase and as noted below for the pups, animals were housed individually in suspended stainless steel cages with deotized cage board in the bedding trays. During gestation and lactation, individual dams (and litters) were housed in polycarbonate cages with corncob bedding. Pups passing vaginal patency and preputial separation were transferred to individual cages.	
Diet:	Purina Mills Rodent Lab Chow 5002 meal, *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature**	18-26°C
	Humidity	30-70%
	Air changes	At least 10/hour
	Light cycle	12 hours light/12 hours dark
Acclimation period:	7 days	

B. PROCEDURES AND STUDY DESIGN

1. **Mating procedure:** Mating was accomplished by co-housing one female with one male for up to 14 consecutive days. During the mating phase, vaginal smears were taken each morning and examined for the presence of sperm and/or internal vaginal plug. The day on which insemination was observed in the vaginal smear was designated as gestation day (GD) 0 for that female. In order to evaluate those females which might have been inseminated

without exhibiting sperm in the vaginal smear or an internal vaginal plug, each remaining female was placed in a polycarbonate nesting cage following the 14-day mating period.

2. **Study schedule:** P generation rats (30/sex/dose group) were fed the test diets beginning 10 weeks prior to mating to produce the F1 litters. Following the 14-day mating period and approximately 22-day gestation period, dams were allowed to deliver and rear the F1 litters until weaning on lactation day (LD) 21. F1 offspring (30/sex/dose group) were selected to be parents of the next generation; however, no details of this selection process (e.g., one pup/sex/litter) were provided. The F1 parents were fed the test diets for approximately six weeks prior to mating to produce the F2 generation, and the F2 pups were maintained after weaning for evaluation of sexual maturation.

3. **Animal assignment:** The P animals were randomly assigned, stratified by body weight, to the test groups shown in Table 1. Only those animals falling within ±20% of the overall mean for each sex were included. The P generation rats were exposed to the 8,000 ppm concentration throughout the first generation. F1 offspring were taken off of the 8,000 ppm diet and given control feed beginning on May 25 through May 27, 2007. On May 28, 2007, the high dose of 8,000 ppm was reduced to 4,000 ppm for the remainder of the study due to severe toxicity resulting in some deaths of the F1 juvenile pups. This dose change for the F1 offspring occurred after weaning, around the time of sexual maturation, prior to start of the second generation (pup age range was 26-38 days old).

TABLE 1. Animal assignment [a]

Test group	Dose (ppm) [b]	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low	150	30	30	30	30
Mid	1000	30	30	30	30
High	8000 (P)/4000 (F1) [c]	30	30	30	30

a Data were obtained from page 19 of MRID 47443293.
b Exposure to the test substance was continuous throughout the study.
c P generation rats were fed the 8000 ppm diets throughout the first generation. F1 offspring were fed the 8000 ppm diets until excessive toxicity/mortality was noticed, at which time they were fed control diets for two days and thereafter fed a 4000 ppm diet. The dose change occurred following weaning but before the second generation. The age range of the pups was 26-38 days.

4. **Dose-selection rationale:** Doses were selected based upon the results of a concurrently submitted one-generation reproductive toxicity study (MRID 47443315). A summary of this study is included in Appendix 2 of this DER.

5. **Test diet preparation and analysis:** each dietary formulation was prepared by mixing the appropriate amount of the test material (adjusted for purity) directly with a portion of the feed at room temperature to form a premix. After mixing for 10 minutes, this premix was mixed with the appropriate amount of additional feed to achieve the desired concentration. The control test diet was taken directly from the bag without mixing. Test diets for each treatment group were prepared weekly (or at greater intervals, if diets available for use were

within stability limits) during the entire study and stored at freezer conditions until presented to the animals. Concentration analyses were performed on samples from each dose level from batches intended for study weeks 1, 2, 3 and at monthly intervals thereafter. Homogeneity and stability of the test material in the dietary formulations were verified at 20 and 10,000 ppm; these concentrations were chosen to bracket those used in this study. For homogeneity analyses, three samples were taken from three layers (top, middle, and bottom) of the mixing bowl for a total of nine samples for each concentration. An average was calculated for each of these 9 concentrations, and this mean was used as the beginning measurement for the stability evaluation. Stability was then determined after 7, 14, 28, and 63 days in the freezer and after 7 days in the freezer followed by 7 days at room temperature.

Additionally, it was noted that the concentration of the test substance in the feed was reduced by 50% for the females during the lactation period (LD 0-21) in order to offset the substantial increase in food consumption normally observed in all dams during this phase. In order to verify that an approximately constant test substance intake (mg/kg body weight/day) was maintained throughout the study, additional concentration analyses were performed on samples from the first batch of this adjusted feed for each dietary level.

Results

Homogeneity: 90-91% mean nominal; 2.9-3.2% RSD

Stability: 102% initial after 63 days frozen (approximately -20°C)
104-106% initial after 7 days in the freezer followed by 7 days at room temperature

Concentration: 102-106% mean nominal; 1.8-4.4% RSD

The analytical data indicate that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** The test material was administered in the diet continuously throughout the study (i.e., P generation adults were fed the test diets *ad libitum* beginning 10 weeks prior to mating, and the selected F1 adults were fed the same test diet concentrations as their parents beginning on post-natal day (PND 21).

C. OBSERVATIONS

1. **Parental animals:** Cage-side observations were performed twice daily (AM and PM) during the work week and once daily on weekends and holidays. Animals exhibiting notable clinical signs during the cage-side checks were removed from the cage for detailed assessment. Additionally, detailed physical examinations were conducted on all animals at least once a week throughout the study. Body weights of the males and unmated females were recorded weekly throughout the study. Additionally in the females, body weights were recorded on GD 0, 6, 13, and 20 and on LD 0, 4, 7, 14, and 21. The reviewers calculated body weight gains for the overall pre-mating period in the males and for the overall pre-mating, gestation (GD 0-20) and lactation (LD 0-21) intervals in the females. Absolute (g/animal/day) and

relative to body weight (g/kg bw/day) food consumption was calculated and reported weekly throughout the pre-mating period for both sexes and additionally in the females for the intervals between body weight measurements during gestation and lactation. Estrous cycle periodicity and duration were determined from vaginal smears taken daily beginning three weeks prior to mating and continuing until positive evidence of mating was observed. Additionally, estrous cycle stage was determined in all females just prior to termination. Sperm enumeration was performed on samples from one testicle and caudal epididymis; and motility and morphology measurements were determined from sperm taken from the distal vas deferens. Sperm motility was measured in all P and F1 males from all groups; whereas sperm counts and morphology were performed only on the control and high dose males from both generations.

2. **Litter observations:** The following litter parameters (X) were recorded (Table 2):

TABLE 2. F_1 / F_2 Litter Observations [a]

Observation	Time of observation (post-natal day)						
	Day 0	Day 4 [b]	Day 4 [c]	Day 7	Day 14	Day 21	Day 0-21
Number of live pups	-	-	-	-	-	-	X
Number of dead pups	-	-	-	-	-	-	X
Pup weight	X	X	X	X	X	X	-
Sex of each pup (M/F)	X	-	-	-	-	-	-
External alterations	X	X	-	X	X	X	-

a Data were obtained from page 23 and from Table 22 on pages 112 and 114 of the study report.
b Pre-culling
c Post-culling
- not recorded

On PND 4, litters with more than 8 pups were culled by random selection to a maximum of 8 pups per litter (4/sex/litter, as near as possible). Sexual maturation (preputial separation and vaginal patency) was recorded during the post-weaning period.

3. **Postmortem observations**

a. **Parental animals:** All surviving parental animals were euthanized by inhalation of carbon dioxide and subjected to a gross necropsy. The males were terminated as soon as possible after the last litters were produced, and dams were euthanized following the weaning of their litters on LD 22. The uterus was excised, and any implantation sites were counted. Females showing positive evidence of mating but not delivering a litter were sacrificed after GD 24. Any dam not exhibiting positive evidence of mating or delivering a litter was killed following at least 24 days after the end of the mating period. Additionally, patency of the cervical/uterine opening was examined in the females not delivering a litter via flushing of the uterine horns with 10% buffered formalin.

The following tissues from all P and F1 parents were collected (X) and weighed (XX).

	FEMALE REPRODUCTIVE		MALE REPRODUCTIVE		BOTH SEXES
XX	Cervix	XX	Epididymis	XX	Brain
XX	Ovary	XX	Epididymis cauda	XX	Pituitary
X	Oviduct	XX	Coagulating gland	XX	Liver
XX	Uterus	XX	Prostate	XX	Kidney
XX	Vagina	XX	Seminal vesicle	XX	Spleen
		XX	Testis	XX	Thyroid
				XX	Thymus
				XX	Adrenal
				X	Lung
				X	Gross lesions

a Data were obtained from pages 24, 640, and 744 of the study report.

These tissues were fixed in 10% buffered formalin, with the exception of the ovaries and each testis not used for sperm analyses, which were preserved in Bouin's fluid. Tissues were processed routinely, stained with hematoxylin and eosin, and, with the exceptions of the brain, thyroid, and thymus were microscopically examined in the control and high dose groups. Additionally, selected organs were examined in the intermediate dose groups as follows: liver in the 1000 ppm males and females of both generations and in the 150 ppm P generation males; kidneys in the 1000 ppm P and F1 males; and adrenals in 1000 ppm P and F1 females. Reproductive organs were evaluated for any mating pair that: failed to mate, conceive, sire, or deliver healthy offspring; had an abnormal estrous cycle; or had affected sperm numbers, motility, or morphology. Gross lesions (except for maloccluded teeth) were evaluated microscopically. Additionally, any tissues considered to have possible treatment-related changes were examined in the intermediate dose groups. Non-neoplastic lesions were graded as normal, present, or on a 5-point scale (minimal, mild/slight, moderate, marked, or severe); average severity grades for each dose group were calculated for each finding. A quantitative evaluation of the primordial (preantral) and antral follicles and corpora lutea was conducted on 10 randomly selected F1 control and 8000/4000 ppm females that had viable litters. Five serial sections (300 μm) of each ovary were counted.

b. **Offspring:** Culled pups were killed by decapitation, and the grossly abnormal pups were subjected to a necropsy and subsequently discarded. All other culled pups were discarded without examination. Any pups found dead, stillborn, or terminated in a moribund state underwent a gross necropsy to detect any abnormalities and/or find a cause of death. On PND 21, F1 offspring not selected as parental animals and all F2 pups were euthanized by inhalation of carbon dioxide, subjected to a gross necropsy, and the following tissues were collected (X) and weighed (XX).

	FEMALE REPRODUCTIVE		MALE REPRODUCTIVE		BOTH SEXES
XX	Uterus	X	Testis	XX	Brain
X	Ovary	X	Epididymis	XX	Spleen
X	Vagina	X	Prostate	XX	Thymus
X	Cervix	X	Coagulating gland	X	Gross lesions
X	Oviduct	X	Seminal vesicle		

a Data were obtained from page 25 of the study report.

With the exception of the brain, spleen, and thymus, the above-listed tissues were examined microscopically.

D. DATA ANALYSIS

1. **Statistics:** The following statistical analyses were conducted:

Parameters	Statistical tests
Parametric data Body weights Body weight gains Food consumption	Analysis of variance (ANOVA) was performed. If ANOVA revealed significant differences among groups, Dunnett's test was conducted for pair-wise comparisons of the treated groups with controls.
Non-parametric data Number of estrous cycles Litter size Number of implantation sites	Kruskal-Wallis test was performed. If Kruskal-Wallis revealed significant differences among groups, Dunn test was conducted for pair-wise comparisons of the treated groups with controls.
Non-parametric dichotomous data Fertility and gestation indices	Initially analyzed using Chi-square test, and if significance was observed, a Fisher's exact test with Bonferroni correction was applied to the data.
Terminal body weights Organ weights	Bartlett's test for homogeneity of variance. If variances were homogeneous ($p>0.001$), analysis of variance (ANOVA) was performed. If ANOVA revealed significant differences ($p\leq0.05$) among groups, Dunnett's test was conducted for pair-wise comparisons of the treated groups with controls. If variances were heterogeneous ($p<0.001$), Kruskal-Wallis ANOVA was performed. If Kruskal-Wallis revealed significant differences ($p\leq0.05$) among groups, Mann-Whitney U test was conducted for pair-wise comparisons of the treated groups with controls.
Gross lesions	To the extent possible, the frequency was first examined visually, then, in the event of questionable distribution, by statistical analyses using the Chi-square and Fisher's Exact tests.
Histopathology	Chi-square test followed by a one-tailed Fisher's Exact Test in cases of significant ($p\leq0.05$) Chi-square analysis.
Ovarian follicles and corpora lutea count data	Student's t-test (2-sample equal variance test)

Significance was denoted at $p\leq0.05$ and $p\leq0.01$. The statistical methods were considered appropriate.

2. Indices

Reproductive indices: The following reproductive indices were calculated by the performing laboratory from breeding and parturition records of animals in the study:

Mating index (%) = # inseminated females[1]/# females co-housed x 100

Fertility index (%) = # pregnant females[2]/# inseminated females x 100

Gestation index (%) = # females with live pups/# pregnant females x 100

Offspring viability indices: The following offspring indices were calculated by the performing laboratory from lactation records of litters in the study:

Birth index (%) = total # pups born per litter/total # implantation sites per dam x 100

Live birth index (%) = # live pups born per litter/total # pups per litter x 100

Viability index (%) = # live pups per litter on PND 4 (pre-cull)/# live pups born per litter x 100

Lactation index (%) = # live pups per litter on PND 21/# live pups per litter on PND 4 (post-cull) x 100

Gestation duration = # of whole days from day in which insemination is observed in the vaginal smear (GD 0) to LD 0 (delivery of pups and entry into the computer system)

3. **Historical control data:** Historical control data from studies conducted in the performing laboratory from 1998-2006 were provided on pages 1686-1692 in Attachment III of the study report. Data were comprised of reproductive, litter, sexual maturation, pup body weight, and pup organ weight parameters.

II. **RESULTS:** The P generation animals were fed dietary levels of 0, 150, 1000, or 8000 ppm. F1 offspring were initially fed the same test diet concentrations as their parents. However, due to severe toxicity in the F1 offspring, the high dose of 8,000 ppm was reduced to 4,000 ppm (age range was 26-38 days old).

A. PARENTAL ANIMALS

1. Mortality and clinical signs

1 Includes pregnant females not observed sperm positive or with an internal vaginal plug
2 Includes females which did not deliver, but had implantation sites

a. **Mortality:** There were no mortalities in either generation.

b. **Clinical signs of toxicity:** In the P generation, an increased incidence of coarse tremors was observed in the 8000 ppm females from Weeks 6-17 (8/30 rats; $p \leq 0.05$), gestation (2/28 rats; not significant [NS]), and lactation (4/29 rats; NS) compared to 0 controls. There were no treatment-related clinical observations in the P males or in the F1 generation.

2. **Body weight, body weight gain, and food consumption**

a. **Pre-mating:** Selected body weight, body weight gain, and food consumption data during pre-mating are presented in Tables 3a (P generation) and 3b (F1 generation).

In the P generation, there were no treatment-related effects on body weights or body weight gains in the males. Initial decreases ($p \leq 0.05$) in absolute (↓11%) and relative to body weight (↓14%) food consumption were noted during Week 1 in the 8000 ppm males; however, these decreases were transient and did not affect the body weights or body weight gains. In the 8000 ppm P generation females, body weights were decreased ($p \leq 0.01$) by 7-9% compared to controls beginning on Week 1 and continuing through Week 10, resulting in a decrease of 27% (statistics not performed) in body weight gain (Weeks 0-10) for the pre-mating period. Additionally in the 8000 ppm P dams, absolute food consumption was decreased ($p \leq 0.01$) by 8-21% generally throughout pre-mating. In the 1000 ppm dams, absolute food consumption was decreased by 7-8% ($p \leq 0.01$) compared to controls during Weeks 4, 7, and 8; however, these decreases were minor, sporadic, and did not affect body weights or body weight gains.

In the F1 generation at 8000/4000 ppm, body weights were decreased ($p \leq 0.01$) throughout pre-mating in the males (↓9-21%) and females (↓10-13%). Body weight gains in these animals for the pre-mating period were comparable to controls. Relative food consumption for the overall (Weeks 1-10) pre-mating period was decreased ($p \leq 0.01$) by 17% in the males at this dose, and absolute food consumption was generally decreased (↓7-11%; $p \leq 0.05$) throughout pre-mating in the females, with a decrease of 7% ($p \leq 0.01$) in absolute food consumption for the overall (Weeks 1-10) pre-mating period in the females.

TABLE 3a. Mean (±SE) body weights, body weight gains, and food consumption in the P generation during pre-mating [a]

Observation/study week		Dose Group (ppm)			
		0	150	1000	8000
P generation males					
Body weight (g)	Week 0	257.8 ± 2.95	263.7 ± 2.31	268.0 ± 2.85	266.4 ± 3.08
	Week 14	432.1 ± 6.15	452.6 ± 5.91	456.3 ± 6.62 (↑6)	429.2 ± 6.39
Body weight gain (g)	Weeks 0-14	174.3	188.9	188.3	162.8
Food consumption (g/rat/day)					
	Week 1	23.4 ± 0.52	23.0 ± 0.31	22.8 ± 0.30	20.8 ± 0.71* (↓11)
	Weeks 1-10	22.75	23.19	23.66	22.94
Food consumption (g/kg bw/day)					
	Week 1	90.7 ± 1.75	87.3 ± 1.00	85.2 ± 0.95* (↓6)	78.2 ± 2.22** (↓14)
	Weeks 1-10	67.30	66.20	66.57	68.36
P generation females					
Body weight	Week 0	168.8 ± 1.87	167.5 ± 2.24	167.6 ± 1.82	167.4 ± 1.79
	Week 3	199.3 ± 2.37	196.3 ± 2.84	198.9 ± 2.10	186.0 ± 2.91** (↓7)
	Week 8	231.8 ± 2.73	226.4 ± 3.37	221.8 ± 2.60* (↓4)	211.8 ± 2.79** (↓9)
	Week 10	235.9 ± 2.93	231.2 ± 3.67	230.5 ± 2.64	216.1 ± 2.81** (↓8)
Body weight gain	Weeks 0-10	67.1	63.7	62.9	48.7 (↓27)
Food consumption (g/rat/day)					
	Week 1	15.8 ± 0.25	15.5 ± 0.28	15.3 ± 0.18	12.5 ± 0.35** (↓21)
	Week 4	17.3 ± 0.27	17.1 ± 0.34	16.0 ± 0.24** (↓8)	15.5 ± 0.30** (↓10)
	Week 6	16.6 ± 0.23	16.2 ± 0.25	16.3 ± 0.31	15.3 ± 0.30** (↓8)
	Week 7	17.7 ± 0.31	17.0 ± 0.37	16.2 ± 0.27** (↓8)	15.2 ± 0.26** (↓14)
	Week 8	17.5 ± 0.28	16.9 ± 0.36	16.2 ± 0.28** (↓7)	15.6 ± 0.41** ↓11)
	Weeks 1-10	16.97	16.56	16.16	15.23** (↓10)
Food consumption (g/kg bw/day)					
	Week 1	93.8 ± 1.08	92.7 ± 1.21	91.7 ± 1.22	74.7 ± 2.12** (↓20)
	Weeks 1-10	82.66	81.94	80.44	80.13

a Data (n =30) were obtained from Text Table 6 on page 29 and Tables 2, 3, and 4 on page 49-52, 57, 58, 61, and 62 of the study report. Percent differences from the controls, calculated by the reviewers, are included in parentheses.

* Significantly different from the control group at $p \leq 0.05$

** Significantly different from the control group at $p \leq 0.01$

TABLE 3b. Mean (±SE) body weights, body weight gains, and food consumption in the F1 generation during pre-mating [a]

Parameter/study interval		Dose Group (ppm) 0	150	1000	8000/4000
F1 generation males					
Body weight (g)	Week 0	298.0 ± 5.30	302.2 ± 4.58	298.0 ± 5.60	234.7 ± 5.50** (↓21)
	Week 12	430.9 ± 6.96	444.1 ± 6.53	435.6 ± 7.22	390.7 ± 6.79** (↓9)
	Week 14	446.4 ± 7.09	462.3 ± 7.02	446.6 ± 7.52	401.3 ± 6.92** (↓10)
Body weight gain (g)	Weeks 0-14	148.4	160.1	148.6	166.6
Food consumption (g/rat/day)					
	Week 1	25.2 ± 0.55	25.2 ± 0.34	24.9 ± 0.33	25.0 ± 0.40
	Weeks 1-10	24.03	24.71	23.99	24.04
Food consumption (g/kg bw/day)					
	Weeks 1-10	66.00	66.54	66.01	77.19** (↓17)
F1 generation females					
Body weight (g)	Week 0	189.8 ± 2.76	191.2 ± 2.04	186.3 ± 3.17	164.7 ± 2.08** (↓13)
	Week 9	240.8 ± 3.77	240.8 ± 2.89	233.5 ± 3.30	217.1 ± 2.60** (↓10)
	Week 10	244.2 ± 3.73	243.3 ± 2.87	234.1 ± 3.47	218.0 ± 2.56** (↓11)
Body weight gain (g)	Weeks 0-10	54.4	52.1	47.8	53.3
Food consumption (g/rat/day)					
	Week 1	18.5 ± 0.35	18.4 ± 0.21	17.5 ± 0.32	16.8 ± 0.33** (↓9)
	Week 3	18.1 ± 0.31	18.6 ± 0.25	18.0 ± 0.31	16.8 ± 0.28** (↓7)
	Week 4	18.3 ± 0.31	18.5 ± 0.30	17.4 ± 0.33	16.3 ± 0.37** (↓11)
	Weeks 1-10	17.98	18.07	17.44	16.70** (↓7)
Food consumption (g/kg bw/day)					
	Weeks 1-10	82.48	82.37	82.68	86.40

a Data (n =30) were obtained from Text Table 6 on page 29 and Tables 2, 3, and 4 on page 53-56, 63, and 64 of the study report. Percent differences from the controls, calculated by the reviewers, are included in parentheses.

** Significantly different from the control group at $p \leq 0.01$

b. Gestation: Selected body weight, body weight gain, and food consumption data during gestation are presented in Table 4. In the 8000 ppm P dams, body weights were decreased ($p \leq 0.01$) by 9-15% throughout gestation, resulting in a decrease of 30% ($p \leq 0.01$) in body weight gain for the overall (GD 0-20) gestation period. Similarly in the 8000/4000 ppm F1 dams, body weights were decreased ($p \leq 0.01$) by 10-13% throughout gestation, resulting in a decrease of 19% ($p \leq 0.01$) in body weight gain for the overall (GD 0-20) gestation period. Body weights and body weight gains were unaffected by treatment at 150 and 1000 ppm. There were no effects of treatment on food consumption at any dose in either generation.

TABLE 4. Mean (±SE) body weights, body weight gains, and food consumption during gestation [a]					
Parameter/study interval		Dose Group (ppm)			
		0	150	1000	8000/4000 [b]
P generation females					
Body weight (g)	GD 0	238.7 ± 3.01	235.2 ± 3.59	230.2 ± 3.16	217.8 ± 3.46** (↓9)
	GD 6	256.3 ± 2.96	252.9 ± 3.52	246.1 ± 3.16	232.1 ± 3.82** (↓9)
	GD 13	275.7 ± 3.21	273.4 ± 3.52	266.9 ± 4.35	245.6 ± 4.03** (↓11)
	GD 20	334.8 ± 4.30	333.1 ± 5.13	331.4 ± 4.94	285.4 ± 5.83** (↓15)
Body weight gain (g)	GD 0-20	96.1 ± 2.64	97.9 ± 2.74	101.2 ± 3.07	67.6 ± 3.07** (↓30)
Food consumption (g/rat/day)	GD 0-20	19.43	19.67	19.23	18.43
Food consumption (g/kg bw/day)	GD 0-20	75.49	77.93	77.73	79.77
F1 generation females					
Body weight (g)	GD 0	242.0 ± 4.21	244.4 ± 3.04	231.6 ± 2.88	217.4 ± 2.64** (↓10)
	GD 6	258.0 ± 4.34	258.6 ± 2.95	246.7 ± 3.30	232.8 ± 2.43** (↓10)
	GD 13	277.1 ± 4.21	277.3 ± 3.23	266.6 ± 3.24	247.2 ± 2.51** (↓11)
	GD 20	337.2 ± 4.97	337.0 ± 4.38	322.9 ± 3.09	294.5 ± 3.57** (↓13)
Body weight gain (g)	GD 0-20	95.3 ± 2.30	92.6 ± 2.54	91.3 ± 1.98 (↓4)	77.1 ± 3.05** (↓19)
Food consumption (g/rat/day)	GD 0-20	20.20	18.83	19.00	20.87
Food consumption (g/kg bw/day)	GD 0-20	78.37	72.40	74.63	87.00

a Data (n =30) were obtained from Text Table 7 on pages 30-31 and Table 8 on pages 77-78 of the study report. Percent differences from the controls, calculated by the reviewers, are included in parentheses.

b P generation dams received 8000 ppm diets; F1 generation dams received 4000 ppm diets.

** Significantly different from the control group at $p \leq 0.01$

c. **Lactation:** Selected body weight, body weight gain, and food consumption data during lactation are presented in Table 5. Body weights were decreased ($p \leq 0.01$) throughout lactation in the 8000 ppm P dams (↓13-17%) and in the 8000/4000 ppm F1 dams (↓8-14%). Absolute food consumption for the overall (LD 0-21) lactation period was decreased by 10-12% in the 8000/4000 ppm animals. There were no other effects of treatment on body weights, body weight gains, or relative food consumption.

TABLE 5. Mean (±SE) body weights, body weight gains, and food consumption during lactation [a]					
Parameter/study interval		Dose Group (ppm)			
		0	150	1000	8000/4000 [b]
P generation females					
Body weight (g)	LD 0	260.4 ± 4.62	258.2 ± 3.70	254.8 ± 3.79	221.2 ± 4.38** (↓15)
	LD 4	271.2 ± 2.80	267.8 ± 3.73	265.6 ± 3.24	235.5 ± 4.18** (↓13)
	LD 7	282.1 ± 2.75	278.0 ± 3.89	272.2 ± 3.26	244.1 ± 4.42** (↓13)
	LD 14	297.3 ± 3.59	290.6 ± 3.55	288.0 ± 3.57	247.1 ± 5.04** (↓17)
	LD 21	289.3 ± 3.69	281.0 ± 5.10	283.6 ± 3.34	252.5 ± 5.27** (↓13)
Body weight gain (g)	LD 0-21	28.9	22.8	28.8	31.3
Food consumption (g/rat/day)	LD 0-21	45.90	46.70	44.70	40.25** (↓12)
Food consumption (g/kg bw/day)	LD 0-21	164.00	169.35	164.25	168.78
F1 generation females					
Body weight (g)	LD 0	263.3 ± 4.28	265.0 ± 3.75	256.1 ± 3.60	231.0 ± 2.96** (↓12)
	LD 4	273.0 ± 3.97	273.0 ± 3.29	262.9 ± 3.73	240.7 ± 2.86** (↓14)
	LD 7	281.9 ± 3.75	280.5 ± 3.35	272.4 ± 3.47	253.0 ± 2.72** (↓10)
	LD 14	295.2 ± 4.22	290.7 ± 3.78	285.4 ± 3.25	266.0 ± 2.65** (↓10)
	LD 21	279.7 ± 4.61	281.8 ± 3.33	274.5 ± 3.19	256.2 ± 3.12** (↓8)
Body weight gain (g)	LD 0-21	16.4	16.8	18.4	25.2
Food consumption (g/rat/day)	LD 0-21	48.58	46.95	44.78	43.93** (↓10)
Food consumption (g/kg bw/day)	LD 0-21	173.48	168.60	165.40	176.38

a Data (n =30) were obtained from Text Table 8 on page 32 of the study report. Percent differences from the controls, calculated by the reviewers, are included in parentheses.

b P generation dams received 8000 ppm diets; F1 generation dams received 4000 ppm diets.

** Significantly different from the control group at $p \leq 0.01$

3. **Test substance intake:** Test substance intake during pre-mating was calculated as follows:

Chemical intake (mg/kg/day) = mean analytical concentration. (ppm) x mean weekly relative to body weight food consumption (g/kg bw/day)/1000

The mean test substance intake for both generations during pre-mating is considered to be representative of the achieved intake for the entire study (Table 6). For the high dose, separate dose levels were used for P and offspring due to halving of the dose for F1 offspring.

TABLE 6. Mean test substance intake (mg/kg/day in males/females) during pre-mating [a]				
Generation	Dose (ppm)			
	0	150	1000	8000/4000 [b]
P generation	0/0	10.2/12.6	68.9/83.2	560.1/656.2
F1 generation	0/0	10.6/13.1	69.6/87.2	317.6/355.5
Mean [c]	**0/0**	**10.4/12.9**	**69.3/85.2**	**438.9/505.9**

a Data were obtained from Text Table 9 on page 33 of the study report.
b P generation dams received 8000 ppm diets; F1 generation dams received 4000 ppm diets.
c Calculated by the reviewers as the average of the P and F1 generations separately for each sex.

4. **Reproductive function**

a. **Estrous cycle length and periodicity:** There were no effects of treatment on estrous cycle duration or periodicity in the P or F1 generation females.

b. **Sperm measures:** There were no effects of treatment on sperm motility, counts, or morphology in either generation.

c. **Ovarian follicle counts:** There were no treatment-related effects on ovarian follicle counts. The numbers of preantral follicles and antral follicles in the 4000 ppm F1 dams were comparable to the controls. The mean number of corpora lutea in the 4000 ppm F1 dams was 23% lower than controls; however, this decrease was not statistically significant and was not associated with abnormal morphological changes. Furthermore, because reproductive performance was not affected in these animals, this minor decrease was not considered adverse.

5. **Reproductive performance:** The mating, fertility, and gestation indices in the treated groups were comparable to controls in both generations (Table 7). There were no effects of treatment on the pre-coital interval or gestation duration in either generation.

TABLE 7. Reproductive performance [a]				
Parameter	Dose Group (ppm)			
	0	150	1000	8000/4000 [b]
P generation				
Pre-coital interval (days), mean ± SE	2.8 ± 0.56	2.2 ± 0.21	3.0 ± 0.59	2.7 ± 0.42
Number paired	30	30	30	30
Number mated	30	30	29	30
Number of animals delivering	27	29	26	29
Number of animals with implantations	28	29	26	29
Mating index (%)	100	100	96.7	100
Fertility index (%)	93.9	96.7	89.7	96.7
Gestation index (%)	96.4	100	100	100
Gestation duration (days), mean ± SE	21.8 ± 0.11	21.9 ± 0.08	21.8 ± 0.11	22.0 ± 0.07
median	22.0	22.0	22.0	22.0
F1 generation				
Pre-coital interval (days), mean ± SE	3.1 ± 0.21	2.6 ± 0.26	2.5 ± 0.41	2.5 ± 0.20
Number paired	30	30	30	30
Number mated	30	30	30	30
Number of animals delivering	27	30	28	29
Number of animals with implantations	27	30	28	29
Mating index (%)	100	100	100	100
Fertility index (%)	90	100	93.3	96.7
Gestation index (%)	100	100	100	100
Gestation duration (days), mean ± SE	22.1 ± 0.12	22.0 ± 0.08	21.9 ± 0.10	21.9 ± 0.10
median	22.0	22.0	22.0	22.0

a Data were obtained from Text Table 11 on page 35 and Table 6 on pages 73 and 74 of the study report.
b P generation dams received 8000 ppm diets; F1 generation dams received 4000 ppm diets.

6. Parental postmortem results

a. Organ weights: At 1000 ppm, increases ($p \leq 0.05$) were found in absolute (↑14%) and relative to body weight (↑8%) liver weights in the P generation males (Table 8). In the P males, absolute weight of the left adrenal was increased ($p \leq 0.05$) by 11-15% at 1000 ppm and above; however, the relative weight of the right adrenal was decreased ($p \leq 0.05$) by 17% at 8000/4000 ppm compared to controls. Because of the lack of bilateral consistency in the effects on the adrenal weights and the lack of corroborating histopathology in this group, these differences were considered incidental. Additionally in the 8000/4000 ppm group, the following organ weights were significantly increased ($p \leq 0.05$) over controls: (i) absolute liver weights in the P males (↑20%); (ii) relative liver weights in the P males (↑21%) and females (↑12%) and F1 males (↑12%) and females (↑8%); and (iii) absolute and relative kidney weights in the P males (↑7-9%). Several other organ weights in the P females and F1 males and females differed significantly ($p \leq 0.05$) from controls but were considered unrelated to treatment because they were not corroborated by microscopic findings that would indicate a treatment-related effect and were likely attributed to the decreased ($p \leq 0.05$) terminal body weights in these animals (↓9-11%).

TABLE 8. Selected mean (±SE) absolute (g) and relative to body weight (%) organ weights in the parents [a]

Parameter		Dose Group (ppm)			
		0	150	1000	8000/4000 [b]
P generation males					
Terminal body weight (g)		439.8 ± 34.5	461.0 ± 32.6	464.6 ± 35.4* (↑6)	436.7 ± 35.7
Liver,	absolute	14.299 ± 1.687	15.324 ± 1.676	16.295 ± 1.930* (↑14)	17.158 ± 1.789* (↑20)
	relative	3.245 ± 0.219	3.323 ± 0.256	3.507 ± 0.323* (↑8)	3.932 ± 0.288* (↑21)
Adrenals, right,	absolute	0.026 ± 0.004	0.027 ± 0.004	0.028 ± 0.005	0.029 ± 0.005
	relative	0.006 ± 0.001	0.006 ± 0.001	0.006 ± 0.001	0.007 ± 0.001* (↓17)
Adrenals, left,	absolute	0.027 ± 0.003	0.029 ± 0.005	0.030 ± 0.005* (↑11)	0.031 ± 0.005* (↑15)
	relative	0.006 ± 0.001	0.006 ± 0.001	0.007 ± 0.001*	0.007 ± 0.001*
Kidneys, left	absolute	1.393 ± 0.172	1.432 ± 0.170	1.496 ± 0.172	1.508 ± 0.168* (↑8)
	relative	0.316 ± 0.028	0.310 ± 0.028	0.322 ± 0.026	0.346 ± 0.030* (↑9)
Kidneys, right	absolute	1.462 ± 0.153	1.487 ± 0.158	1.558 ± 0.189	1.558 ± 0.177 (↑7)
	relative	0.333 ± 0.025	0.323 ± 0.028	0.335 ± 0.032	0.357 ± 0.029* (↑7)
P generation females					
Terminal body weight (g)		283.6 ± 22.7	278.2 ± 27.8	277.8 ± 19.5	251.1 ± 28.8* (↓11)
Liver,	absolute	13.097 ± 1.885	13.013 ± 1.950	13.015 ± 1.972	12.977 ± 2.081
	relative	4.608 ± 0.484	4.659 ± 0.399	4.671 ± 0.549	5.159 ± 0.487* (↑12)
F1 generation males					
Terminal body weight (g)		455.0 ± 39.4	468.6 ± 39.4	450.3 ± 41.1	406.8 ± 39.5* (↓11)
Liver,	absolute	15.499 ± 1.810	15.760 ± 1.893	15.627 ± 1.845	15.577 ± 1.872
	relative	3.404 ± 0.272	3.359 ± 0.232	3.469 ± 0.261	3.827 ± 0.244* (↑12)
F1 generation females					
Terminal body weight (g)		289.7 ± 23.9	295.8 ± 17.6	284.3 ± 18.4	265.0 ± 18.3* (↓9)
Liver,	absolute	14.562 ± 2.577	15.461 ± 1.460	14.466 ± 1.868	14.315 ± 1.974
	relative	5.008 ± 0.688	5.227 ± 0.380	5.077 ± 0.493	5.393 ± 0.627* (↑8)

a Data were obtained from Tables OW1K-SUM, OW2K-SUM, OW3K-SUM, and OW4K-SUM on pages 661-663, 666, 669, 671, 672, 674, 676, and 679 of the study report.
b P generation dams received 8000 ppm diets; F1 generation dams received 4000 ppm diets.
* Significantly different from the control group at $p \leq 0.05$

b. Pathology

1) **Macroscopic examination**: There were no treatment-related gross findings in the P or F1 males or females.

2) **Microscopic examination**: Incidences (# affected/30) of the following microscopic findings were increased ($p \leq 0.05$) in the 8000/4000 ppm group, compared to 0 controls, unless otherwise stated (Table 9): (i) liver hypertrophy in the P generation males (27 treated vs 3 controls) and females (30) and at 4000 ppm in the F1 males (15) and females (30); (ii) hyaline degeneration in the kidneys in the males in the P generation (15) and F1 generation (6); (iii) tubular regeneration in the kidneys in the P generation males (13 treated vs 3 controls); and (iv) adrenal gland vacuolization in the P females (15 treated vs 1 control). An increase in the incidence of liver hypertrophy was also noted in the 1000 ppm P males (8/30 treated vs 3/30 controls); however, this increase was slight and not statistically significant.

There were no other treatment-related microscopic findings in the males or females of either generation.

TABLE 9. Incidences, # affected, and mean severity of selected histopathology findings in the parents [a]

Parameter	Dose Group (ppm)			
	0	150	1000	8000/4000 [b]
P generation males				
Liver, # examined	30	30	30	30
Hypertrophy	3 (1.0)	1 (1.0)	8 (1.3)	27* (1.7)
Kidneys, # examined	30	2	30	30
Degeneration, hyaline	---	---	1 (1.0)	15* (1.5)
Regeneration, tubular	3 (1.0)	---	5 (1.0)	13* (1.3)
P generation females				
Liver, # examined	30	---	30	30
Hypertrophy	---	---	---	30* (1.6)
Adrenal gland, # examined	30	---	30	30
Vacuolization	1 (1.0)	---	1 (1.0)	15* (1.1)
F1 generation males				
Liver, # examined	30	---	30	30
Hypertrophy	---	---	---	15* (1.6)
Kidneys	30	3	30	30
Degeneration, hyaline	---	---	---	6* (1.2)
F1 generation females				
Liver, # examined	30	---	30	30
Hypertrophy	---	---	---	30* (2.2)

a Data were obtained from Tables MP 1-SUM, on pages 742-744, 749, and 750 of the study report.
b P generation dams received 8000 ppm diets; F1 generation dams received 4000 ppm diets.
c Average severity scores of animals with lesion: 1 (minimal) to 5 (severe).
--- No animals affected (i.e., zero incidence)
* Significantly different from the control group at $p \leq 0.05$

B. OFFSPRING

1. **Viability and clinical signs:** Litter survival indices for the F1 and F2 litters are included in Table 10. There were no treatment-related effects on the birth, live birth, viability, or lactation indices. Pup sex ratio was unaffected by treatment.

   In the F1 pups, the following clinical signs of toxicity (# pups affected/# litters affected) were observed in the 8000/4000 ppm group vs. 0 controls (Table 11): (i) pups cold to touch (1/1); (ii) perianal stain (15/9); (iii) urine stain (26/11); (iv) weak (2/1); (v) labored breathing (1/1); (vi) nasal stain (9/6); (vii) tremors (20/9); (viii) increased reactivity (2/1); (ix) distended abdomen (53/22); (x) increased activity (28/14); (xi) myoclonus (2/1); (xii) diarrhea (2/2); and (xiii) soft stool (3/3). No clinical signs of toxicity were noted in the F2 pups.

TABLE 10. Litter parameters [a]				
Parameter	Dose Group (ppm)			
	0	150	1000	8000/4000 [b]
F1 litter				
Mean (±SE) implantation sites	11.2 ± 0.58	11.9 ± 0.47	11.7 ± 0.50	10.6 ± 0.57
Number born live	290	327	290	296
Number stillborn	3	1	2	2
Mean litter size PND 0	10.9 ± 0.53	11.3 ± 0.48	11.2 ± 0.52	10.3 ± 0.59
Birth index (%)	89.9 ± 3.91	95.1 ± 1.53	96.1 ± 2.03	96.6 ± 1.38
Live birth index (%)	98.9 ± 0.80	99.8 ± 0.22	99.3 ± 0.51	99.5 ± 0.35
Viability index (%)	99.1 ± 0.67	99.2 ± 0.57	94.4 ± 3.61	99.2 ± 0.58
Lactation index (%)	99.5 ± 0.46	99.6 ± 0.43	99.5 ± 0.48	99.1 ± 0.60
Sex ratio on PND 0 (%♂)	47.3 ± 2.67	50.0 ± 2.44	44.0 ± 2.86	51.2 ± 3.93
F2 litter				
Mean (±SE) implantation sites	11.5 ± 0.34	11.1 ± 0.39	11.0 ± 0.34	9.9 ± 0.53
Number born live	294	315	290	268
Number stillborn	1	2	0	2
Mean litter size PND 0	10.9 ± 0.32	10.6 ± 0.38	10.4 ± 0.39	9.3 ± 0.54
Birth index (%)	95.2 ± 1.22	95.3 ± 1.36	93.6 ± 1.91	93.7 ± 1.79
Live birth index (%)	99.0 ± 0.78	99.3 ± 0.46	100.0 ± 0.00	97.9 ± 1.75
Viability index (%)	95.7 ± 3.70	99.3 ± 0.47	96.3 ± 2.13	95.1 ± 3.47
Lactation index (%)	99.0 ± 0.96	99.1 ± 0.62	100.0 ± 0.00	100.0 ± 0.00
Sex ratio on PND 0 (%♂)	48.8 ± 3.21	51.1 ± 3.58	51.4 ± 2.85	48.1 ± 3.64

a Data were obtained from Text Table 12 on page 38, Table 6 on pages 73-74 and Table 22 on pages 112-115 of the study report.

b P generation dams received 8000 ppm diets; F1 generation dams received 4000 ppm diets.

TABLE 11. Clinical signs of toxicity in F1 offspring during PND 22-61 (# pups affected/# litters affected) [a]

Parameter	Dose Group (ppm)			
	0	150	1000	8000/4000 [b]
F1 litter				
Number of liveborn pups	290	327	290	296
Number of litters with liveborn pups	27	29	26	29
Pups cold to touch	---	---	---	1/1
Perianal stain	---	---	---	15/9
Urine stain	---	---	---	26/11
Weak	---	---	---	2/1
Labored breathing	---	---	---	1/1
Nasal stain	---	---	1/1	9/6
Tremors	---	---	---	20/9
Increased reactivity	---	---	---	2/1
Distended abdomen	---	---	---	53/22
Increased activity	---	---	---	28/14
Myoclonus (Jerking movement)	---	---	---	2/1
Diarrhea	---	---	---	2/2
Soft stool	---	---	---	3/3

a Data were obtained from Table 18 on page 97 of the study report.

b P generation rats were fed the 8000 ppm diets throughout the first generation. F1 offspring were fed the 8000 ppm diets until excessive toxicity/mortality was noticed, at which time they were fed control diets for two days and thereafter fed a 4000 ppm diet. The dose change occurred following weaning but before the second generation. The age range of the pups was 26-38 days.

--- No animals affected (i.e., zero incidence)

2. **Body weight:** Pup body weight data are presented in Table 12. At 8000/4000 ppm, F1 pup body weights were decreased by 12-22% ($p \leq 0.01$) compared to controls throughout the post-natal period for males and females. Body weight gains for the overall post-natal period (PND 1-21) at this dose were decreased by 22-24% (statistics not performed). Pup body weights and body weight gains were comparable to controls in the F1 generation at 150 and 1000 ppm and in all treated groups in the F2 offspring.

TABLE 12. Pup body weights [a]				
	Dose Group (ppm)			
Parameter/Post natal day (PND)	0	150	1000	8000/4000 [d]
F1 males				
Body weight, PND 1	6.0 ± 0.11	6.1 ± 0.07	6.0 ± 0.11	5.7 ± 0.11
PND 4 [b]	9.8 ± 0.28	9.9 ± 0.18	9.9 ± 0.23	8.5 ± 0.26** (↓13)
PND 4 [c]	9.8 ± 0.28	9.9 ± 0.19	10.0 ± 0.23	8.4 ± 0.26** (↓14)
PND 7	15.6 ± 0.37	16.0 ± 0.26	16.0 ± 0.31	12.9 ± 0.38** (↓17)
PND 14	33.3 ± 0.56	33.2 ± 0.44	33.2 ± 0.50	26.3 ± 0.85** (↓21)
PND 21	50.1 ± 0.85	49.8 ± 0.89	49.9 ± 0.79	39.0 ± 1.31** (↓22)
Body weight gain, PND 1-21	44.1	43.7	43.9	33.3 (↓24)
F1 females				
Body weight, PND 1	5.6 ± 0.10	5.8 ± 0.09	5.6 ± 0.10	5.4 ± 0.10
PND 4 [b]	9.3 ± 0.26	9.6 ± 0.21	9.5 ± 0.26	8.2 ± 0.23** (↓12)
PND 4 [c]	9.4 ± 0.27	9.7 ± 0.22	9.4 ± 0.27	8.2 ± 0.23** (↓13)
PND 7	15.0 ± 0.34	15.5 ± 0.35	15.1 ± 0.37	12.6 ± 0.38** (↓16)
PND 14	32.3 ± 0.49	32.5 ± 0.56	31.5 ± 0.67	25.7 ± 0.80** (↓20)
PND 21	48.2 ± 0.74	48.4 ± 0.96	47.1 ± 0.76	38.5 ± 1.28** (↓20)
Body weight gain, PND 1-21	42.6	42.6	41.5	33.1 (↓22)
F2 males				
Body weight, PND 1	6.1 ± 0.09	6.3 ± 0.05	6.1 ± 0.12	6.2 ± 0.13
PND 4 [b]	10.1 ± 0.19	10.6 ± 0.19	9.8 ± 0.34	10.0 ± 0.30
PND 4 [c]	10.1 ± 0.20	10.5 ± 0.19	9.8 ± 0.34	10.0 ± 0.31
PND 7	16.3 ± 0.33	16.8 ± 0.30	15.7 ± 0.54	15.8 ± 0.48
PND 14	33.3 ± 0.53	33.8 ± 0.53	32.4 ± 0.78	32.0 ± 0.96
PND 21	50.6 ± 0.82	51.6 ± 0.90	48.5 ± 1.00	47.6 ± 1.36
Body weight gain, PND 1-21	44.5	45.3	42.4	41.4
F2 females				
Body weight, PND 1	5.8 ± 0.09	5.9 ± 0.07	5.8 ± 0.10	5.8 ± 0.11
PND 4 [b]	9.7 ± 0.18	10.1 ± 0.20	9.5 ± 0.31	9.5 ± 0.25
PND 4 [c]	9.6 ± 0.18	10.2 ± 0.20	9.5 ± 0.31	9.5 ± 0.25
PND 7	15.6 ± 0.29	16.1 ± 0.30	15.2 ± 0.48	15.1 ± 0.41
PND 14	32.3 ± 0.45	32.7 ± 0.51	31.2 ± 0.70	30.8 ± 0.78
PND 21	48.4 ± 0.61	48.7 ± 0.82	46.1 ± 0.87	45.6 ± 1.01* (↓6)
Body weight gain, PND 1-21	42.6	42.8	40.3	39.8

a Data were obtained from Text Tables 13b and 13c and Table 20 on pages 39, 40, and 100-105 of the study report. Percent differences from the controls, calculated by the reviewers, are included in parentheses.
b Pre-culling
c Post-culling
d P generation dams received 8000 ppm diets; F1 generation dams received 4000 ppm diets.
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

3. **Sexual maturation:** Sexual maturation was significantly ($p \leq 0.05$) delayed in both sexes from both generations at 8000/4000 ppm compared to controls (Table 13). The mean age at preputial separation in the F1 generation at this dose was 51.8 days compared to 42.5 days in the controls. In the F2 generation, preputial separation occurred after an average of 46.6 days compared to 43.2 days. The mean age at vaginal opening occurred at 40.9 days compared to 34.1 days in the F1 generation, and at 36.8 days vs 34.4 days in the F2 offspring. The percentage of pups reaching criterion (97-100%) was unaffected by treatment.

TABLE 13. Sexual maturation [a]				
Parameter	Dose Group (ppm)			
	0	150	1000	8000/4000
F1 generation				
Preputial separation, mean ± SE (days)	42.5 ± 0.35	43.1± 0.41	42.8 ± 0.49	51.8 ± 0.85**
Pups reaching criterion (%)	100	100	100	100
Vaginal opening, mean ± SE (days)	34.1 ± 0.71	34.7 ± 0.84	35.3 ± 0.94	40.9 ± 1.10**
Pups reaching criterion (%)	97	97	97	100
F2 generation				
Preputial separation, mean ± SE (days)	43.2 ± 0.40	43.5 ± 0.57	43.4 ± 0.38	46.6 ± 0.71**
Pups reaching criterion (%)	100	100	100	100
Vaginal opening, mean ± SE (days)	34.4 ± 0.80	33.8 ± 0.67	33.7 ± 0.46	36.8 ± 0.52*
Pups reaching criterion (%)	100	100	100	100

a Data were obtained from Table 23 on pages 116-117 of the study report; n = 25-29.
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

4. Offspring postmortem results

a) **Organ weights:** There were no treatment-related effects on organ weights in the F1 or F2 pups. Terminal body weights were decreased in the pups of both sexes from both generations. With the exception of the F2 males, these decreases were statistically significant ($p \leq 0.05$). Absolute brain weights were decreased in the F1 males ($p \leq 0.05$) and females (NS), and relative brain weights were increased in both sexes from both generations. Additionally in the F1 males and females, absolute thymus weights were decreased ($p \leq 0.05$). These differences ($p \leq 0.05$) were likely related to the decreased terminal body weights in these pups. Decreases were also observed in both the absolute and the relative spleen weights in the F1 and F2 males and females, indicating that the spleen weight was decreased to a greater extent than could be accounted for by lower body weight alone. These decreases may be the result of decreased growth and development of the weanlings. Furthermore, there were no corroborating gross or microscopic lesions in these organs.

b) **Pathology**

1) **Macroscopic examination:** No macroscopic findings could be attributed to treatment in the F1 or F2 pups.

2) **Microscopic examination:** There were no treatment-related microscopic findings in the F1 or F2 pups.

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** It was concluded that the parental LOAEL was 1000 ppm based on increased liver weights and centrilobular hypertrophy in the P males and on decreased body weights and food consumption in the P females. The reproductive LOAEL was 8000/4000 ppm based on the decreased numbers of implantations and corpora lutea and smaller litter size considered to be secondary to the severe toxicity in these females as pups.

B. **REVIEWER COMMENTS**

1. **PARENTAL ANIMALS:** There were no mortalities in either generation, and there were no treatment-related gross findings at necropsy.

   In the 8000 ppm P generation females, body weights were decreased ($p \leq 0.01$) throughout **pre-mating**, resulting in a decrease of 27% (statistics not performed) in body weight gain for the pre-mating period (Weeks 0-10). Additionally in these animals, absolute food consumption was decreased ($p \leq 0.01$) generally throughout pre-mating.

   In the F1 generation at 4000 ppm, body weights were decreased ($p \leq 0.01$) throughout pre-mating in both sexes. These decreases were greatest at Week 0 and lessened as time progressed, and body weight gains for the pre-mating period were comparable to controls, indicating that the decreased body weights in these animals were due to their decreased weights as pups. Relative food consumption in the males was decreased ($p \leq 0.01$) for the overall (Weeks 1-10) pre-mating period. Absolute food consumption was generally decreased ($p \leq 0.05$) throughout pre-mating in the females, with a decrease of 7% ($p \leq 0.01$) in absolute food consumption for the overall (Weeks 1-10) pre-mating period.

   At 8000 ppm, body weights were decreased ($p \leq 0.01$) throughout **gestation** in the both generations, resulting in decreases ($p \leq 0.01$) in body weight gain for the overall gestation period of 30% and 19% compared to controls in the P and F1 generations, respectively. Body weights and absolute food consumption were decreased ($p \leq 0.01$) throughout **lactation** in both generations, although body weight gains were unaffected by treatment for this interval.

   Increased ($p \leq 0.05$) incidences of liver hypertrophy were observed at 8000 ppm in the P males (27/30 treated vs 3/30 controls) and females (30/30 females vs 0/30 controls) and F1 males (15/30 vs 0/30 controls) and females (30/30 treated vs 0/30 controls). An increase in the incidence of liver hypertrophy was also noted in the 1000 ppm P males (8/30 treated vs 3/30 controls); however, this increase was slight and not statistically significant. Increases ($p \leq 0.05$) were observed in absolute and relative liver weights in the P males at 1000 ppm and above, and in relative liver weights in the P females and F1 males and females in the 8000 ppm group.

In the 8000 ppm males, absolute and relative kidney weights were increased ($p \leq 0.05$) in the P generation. Hyaline degeneration in the kidneys was found in the P (15/30) and (6/30) F1 males, both compared to 0 controls. Tubular regeneration in the kidneys was observed in the P males (13/30 treated vs 3/30 controls).

In the P generation at 8000 ppm, adrenal gland vacuolization was observed in the females (15/30 treated vs 1/30 control).

The reviewers disagree with the Sponsor's assertion of adverse treatment-related effects at 1000 ppm. The only decreases ($p \leq 0.05$) in body weights at 1000 ppm occurred in the P dams at Week 8 (↓4%) and in the F1 dams on GD 20 (↓4%); and absolute food consumption was only decreased by 7-8% in the P dams on Weeks 4, 7, and 8. These decreases were minor, often unrelated to dose, and not adverse. Furthermore, in the absence of other microscopic findings in the liver, the instances of hepatocellular hypertrophy and increased liver weight at 1000 ppm and above were considered to be an adaptive response to treatment and not adverse.

The LOAEL for parental toxicity is 8000 ppm (equivalent to 560.1/656.2 mg/kg/day in males/females, respectively) based on: decreased body weights, body weight gains, and food consumption in both sexes and effects on the kidneys (tubular degeneration/regeneration; increased kidney weights) in the males. The NOAEL is 1000 ppm (equivalent to 69/85 mg/kg/day in males/females, respectively).

2. **OFFSPRING:** There were no treatment-related effects on pup sex ratio, organ weights, gross pathology, or histopathology, or on the birth, live birth, viability, or lactation indices at any dose in either generation. Although the Sponsor considered the decrease in F2 litter size at this 8000/4000 ppm (9.3) compared to controls (10.9) to be a secondary effect of the toxicity observed in the F1 offspring as pups, this decrease was minor, not statistically significant, and not considered adverse.

   In the F1 pups, the following clinical signs of toxicity (# pups affected/# litters affected) were observed in the 8000/4000 ppm group: (i) pups cold to touch (1/1); (ii) perianal stain (15/9); (iii) urine stain (26/11); (iv) weak (2/1); (v) labored breathing (1/1); (vi) nasal stain (9/6); (vii) tremors (20/9); (viii) increased reactivity (2/1); (ix) distended abdomen (53/22); (x) increased activity (28/14); (xi) myoclonus (2/1); (xii) diarrhea (2/2); and (xiii) soft stool (3/3). No clinical signs of toxicity were noted in the F2 pups.

   At 8000/4000 ppm, F1 pup body weights were decreased by 12-22% ($p \leq 0.01$) compared to controls throughout the post-natal period in both sexes. Body weight gains for the overall post-natal period (PND 1-21) at this dose were decreased by 22-24% (statistics not performed). Pup body weights and body weight gains were comparable to controls in the F1 generation at 150 and 1000 ppm and in all treated groups in the F2 offspring.

Sexual maturation was significantly ($p \leq 0.05$) delayed in both sexes from both generations at 4000 ppm compared to controls. The mean age at preputial separation in the F1 generation at this dose was 51.8 days compared to 42.5 days in the controls. In the F2 generation, preputial separation occurred after an average of 46.6 days compared to 43.2 days. The mean age at vaginal opening occurred at 40.9 days compared to 34.1 days in the F1 generation, and at 36.8 days vs 34.4 days in the F2 offspring. The percentage of pups reaching criterion (97-100%) was unaffected by treatment. The delayed sexual maturation did not appear to be due solely to the decreased offspring body weights, as delays in F1 offspring were 7-9 days and F2 offspring did not show significant body weight decreases. A special study was conducted to evaluate sexual maturation in post-weaning female rats exposed to a metabolite of the test material from PND 22-41 (MRID 47443314); a summary of this non-guideline study is included in Appendix 1 of this DER.

The LOAEL for offspring toxicity is 8000/4000 ppm (equivalent to 317.6/355.2 mg/kg/day in males/females, respectively) based on clinical signs of toxicity and decreased body weights and body weight gains. The NOAEL is 1000 ppm (equivalent to 69/85 mg/kg/day in males/females, respectively).

3. REPRODUCTIVE TOXICITY: As discussed above, sexual maturation was delayed in male and female F1 pups. There were no effects of treatment on: estrous cycle duration or periodicity; follicle counts; the mating, fertility, and gestation indices; pre-coital interval; gestation duration; or sperm motility, counts, or morphology in either generation. Although the mean number of corpora lutea in the 4000 ppm F1 dams was 23% lower than controls, this decrease was not statistically significant and was not associated with abnormal morphological changes. Additionally, the Sponsor noted decreases in the mean number of implantations in the F1 parents at 8000/4000 ppm (9.9) compared to controls (11.5); however, these decreases were minor, not statistically significant, and not considered adverse.

The LOAEL for reproductive toxicity is 8000/4000 ppm (equivalent to 317.6/355.2 mg/kg/day in males/females, respectively), based on delayed sexual maturation in F1 and F2 pups. The NOAEL is 1000 ppm (equivalent to 69/85 mg/kg/day in males/females, respectively).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

IV. STUDY DEFICIENCIES: There were no study deficiencies.

Appendix 1

A Special Study to Evaluate Sexual Maturation in Female Wistar Rats

6-(1-fluoroethyl)-1,3,5-triazine-2,4-diamine (BCS-AA10365) is a major metabolite of BCS-AA10717 (Indaziflam. 98.7% purity). The purpose of this non-guideline sexual maturation study was to determine the potential for BCS-AA10365, administered via oral gavage, to cause delayed sexual maturation (vaginal opening) in female Wistar rats (MRID 47443314). Timed-pregnant females were received from the supplier on gestation day (GD 14) and were not treated with the test material but were used only to obtain their female offspring. The dams were allowed to deliver pups and were maintained with their litter until lactation day (LD) 21. On postnatal day (PND) 21, female pups were randomized into dose groups, with littermates equally distributed among the treatment groups. BCS-AA10365 was administered daily via oral gavage to the 15 Wistar female rats/dose group at concentrations of 0, 18.0, 36.5, 72.9, and 145.8 mg/kg/day along with a positive control (2-Chloro-4,6-Diamino-1,3,5-Triazine [DACT]) at 67.5 mg/kg/day. (Note that the positive control dose was lowered from 135 mg/kg/day to 67.5 mg/kg/day on PND 27 or 28 after animals being off dose for one day. The 135 mg/kg/day dose was considered too high (based on the deaths of two animals); therefore, the decision was made to lower the dose and to give one day off from dosing prior to beginning the 67.5 mg/kg/day dose. Body weight determinations and detailed clinical examinations of each animal were conducted daily throughout the dosing period (PND 22-41) and just prior to necropsy (PND 42). The female pups were observed for vaginal opening from PND 22 through PND 42, and the age at complete vaginal opening was recorded. For those animals where vaginal opening failed to occur prior to necropsy, the age of vaginal opening was recorded as the day after necropsy to determine a mean for each treatment group. All females placed on study were subjected to a gross necropsy; selected organs (adrenals, uterus, and ovaries) were weighed; and selected tissues (pituitary, adrenals, uterus, and ovaries) were preserved.

There were no treatment-related gross findings at necropsy.

Vaginal patency was dose-dependently delayed at 72.9 mg/kg/day (+2.3 days) and 145.8 mg/kg/day (+3.9 days) compared to vehicle controls. The number of days until vaginal opening at 145.8 mg/kg/day (37.07 days) was comparable to the positive controls (37.38).

Additionally at 145.8 mg/kg/day, increased incidences of salivation (7/15 treated vs 0/15 controls) and urine stain (3/15 treated vs 0/15 controls) were observed. At this dose, body weights were decreased by 10% ($p \leq 0.05$) on Day 11 of treatment.

In the positive control group (DACT), two animals died, and body weights were decreased by 7-27% throughout the study compared to controls, with a total body weight gain decrease of 13% ($p \leq 0.05$) compared to controls. Excluding the two dead animals, absolute and relative (to body weight) weights of the ovaries and uterus were decreased by 19-30%, with the decrease in absolute ovary weight being statistically significant ($p \leq 0.05$) compared to controls.

The LOAEL for the metabolite BCS-AA10365 is 72.9 mg/kg/day based on decreased body weights and body weight gains and delayed vaginal patency. The NOAEL is 36.5 mg/kg/day.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

Appendix 2

A dose range-finding reproductive toxicity study in the rat

As this study was intended to be used for dose selection for the definitive reproduction toxicity study, only a summary is provided.

In a one-generation dose range-finding reproduction toxicity study (MRID 47443315), BCS-AA10717 (Indaziflam; 94.5%; Batch #EFIM000511) was administered in the diet to 10 Wistar Han Crl: WI (HAN) rats/sex/dose group at dietary levels of 0, 200, 1,000, 3,000 and 8,000 ppm (equivalent to 0/0, 12.7/14.4, 60.9/71.9, 188.7/211.7, and 514.9/545.7 mg/kg/day in males/females during pre-mating) for one generation with one litter produced. In the P generation, the males were fed the test diets for 13 weeks and the females for 10 weeks prior to mating to produce the F1 litters. Exposure to the test diets was continuous throughout pre-mating, mating, gestation, and lactation. The F1 offspring were euthanized at weaning on post-natal day (PND) 21.

No clinical signs of toxicity were noted in either sex, and no gross findings at necropsy were attributed to treatment. No treatment-related effects on body weight or food consumption were observed in the males at any dose level tested.

In the 8000 ppm females, decreases were observed in: (i) body weights throughout the pre-mating (↓6-14%), gestation (↓5-26%), and lactation (↓7-12%) periods; (ii) absolute and relative (to body weight) food consumption during the pre-mating period (↓8-22%), with initial declines observed during the first weeks and continuing through Week 8; and (iii) terminal body weights (↓7%) and uterine weights (absolute, ↓41%; relative, ↓37%) compared to controls.

Adult male organ weight effects included increased: (i) absolute (↑15-22%) and relative (↑11-22%) liver weights at 3000 and 8000 ppm; (ii) absolute and relative kidney weights at 8000 ppm (↑13%); and relative adrenal weights at 8000 ppm (↑8%).

No clinical signs of toxicity were noted in the pups, and there were no effects of treatment on gross pathology. At 8000 ppm, female pup weights were decreased on PND 21 (↓7%), with body weight gains decreased for PND 7-14 (↓8%) and 14-21 (↓14%). Additionally in the 8000 ppm females, decreases were noted in absolute (↓21%) and relative (↓15%) spleen weights and in absolute (↓19%) and relative (↓13%) uterus weights. There were no treatment-related effects on body weights, body weight gains, or organ weights in the male pups.

There was no evidence of reproductive toxicity. The precoital interval, gestation duration, and numbers of implantations in the treated groups were comparable to controls. The litter size, sex ratio, and birth, live birth, viability, lactation indices in the treated groups were comparable to controls.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.